Anti-Microbial Agents:
Anti-Bacterial Agents:
Sulfonamides Related Drugs

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SECTION 7

Drugs Impacting Infectious and Neoplastic Disease Processes

CHAPTER 29

Drugs Used to Treat Bacterial Infections

Elmer J. Gentry, E. Jeffrey North, and Robin M. Zavod

SaraRAmini Oct 2024

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Drugs covered in this chapter[a]:

ANTIBACTERIALS

Sulfonamide class

- Silver sulfadiazine
- Sulfacetamide
- Sulfamethoxazole
- Sulfisoxazole
- Trimethoprim

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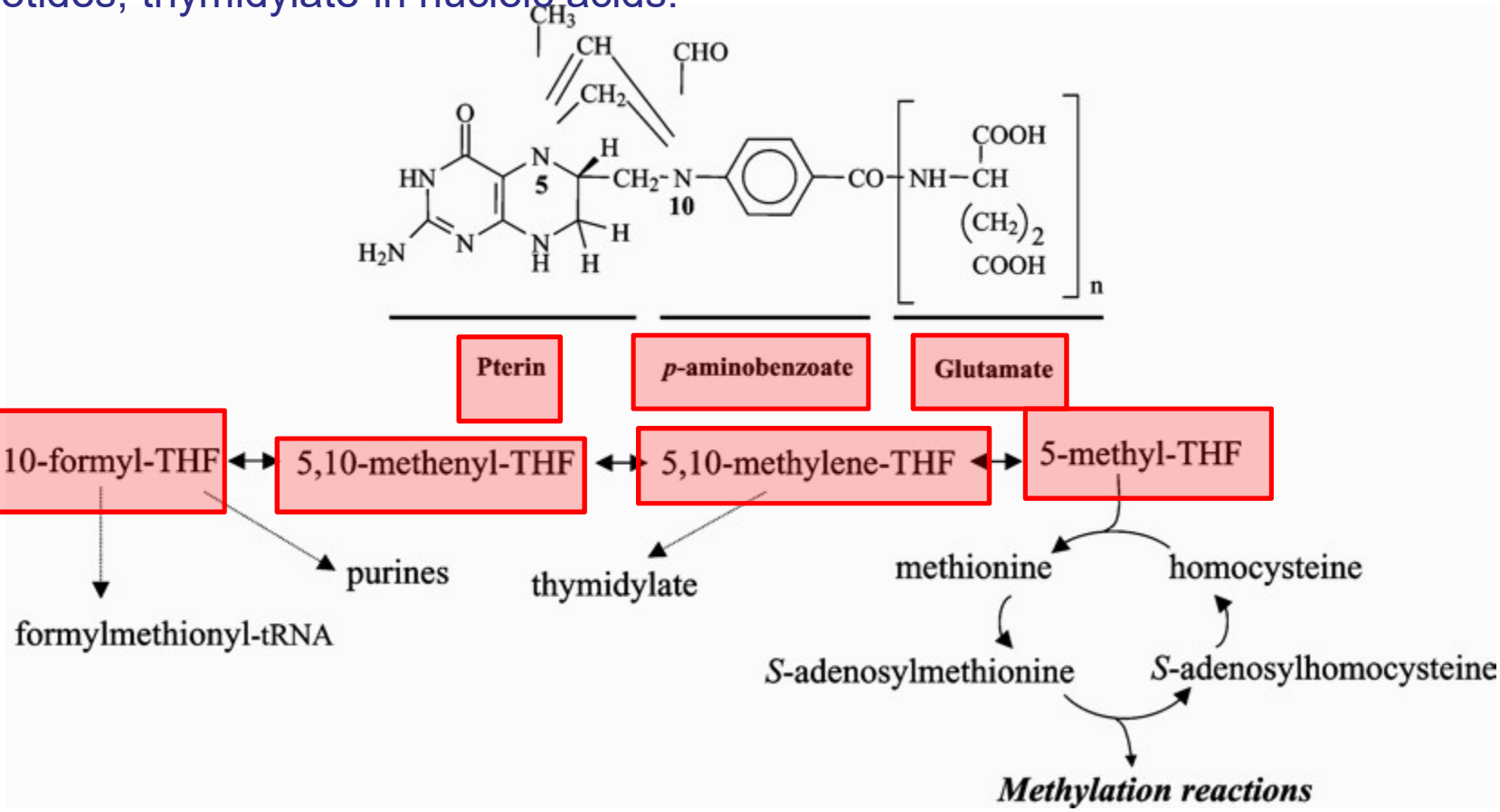
Tetra-Hydrofolic Acid (THF) as a One Carbon Transporter

Folic acid: a factor to transport one-carbon groups

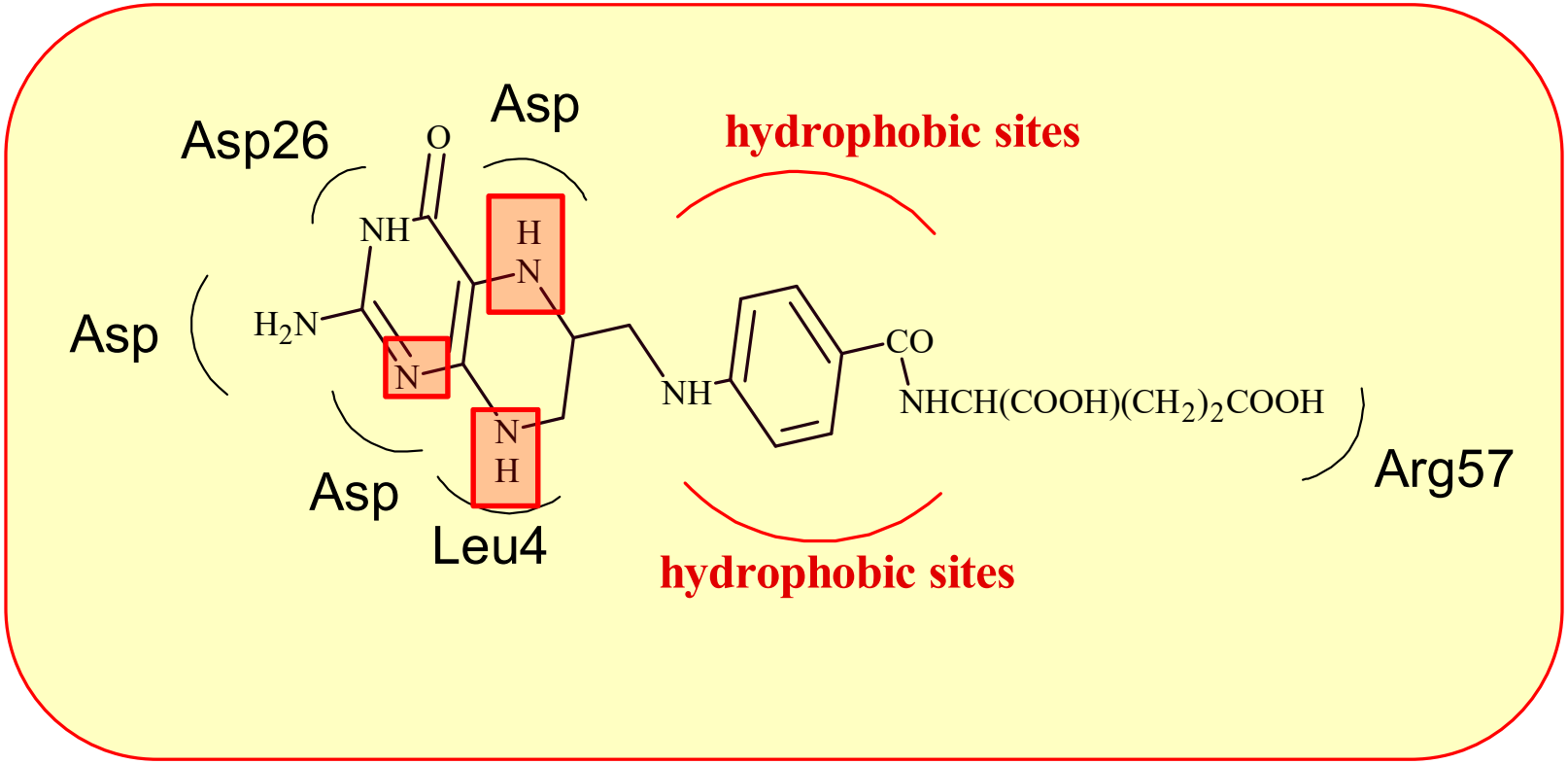
Necessary to synthesize:

✓some purine & pyrimidine

✓nucleotides, thymidylate in nucleic acids.



Interaction Points of Tetra-Hydrofolic Acid in Active Site of DHFR



Two Structural Classes of DHFRI

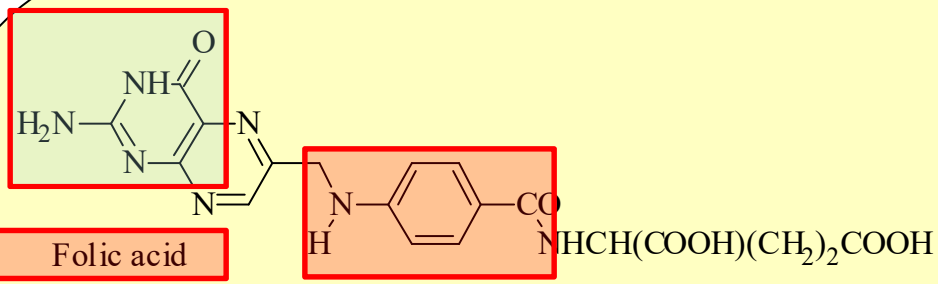
- Classic:
  - ✓ pterine like structures:

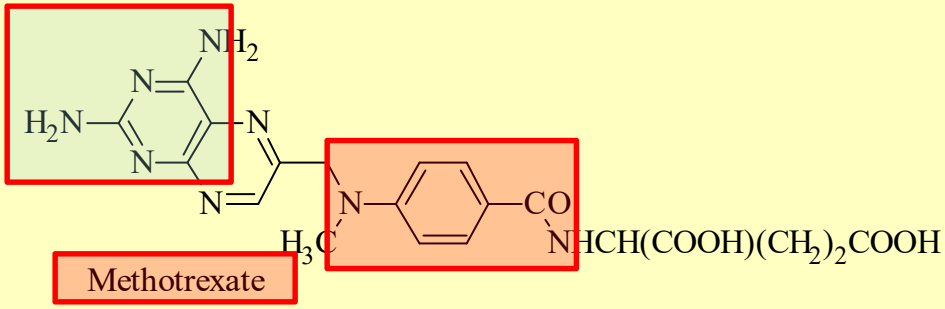
    methotrexate,
    pemetraxate, …
- Non- Classic:
  - ✓ biguanide structures
  - ✓ aryl pyrimidine structures:

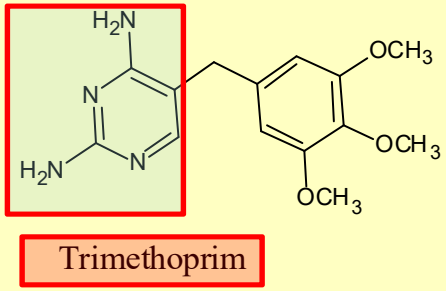
    trimethoprim

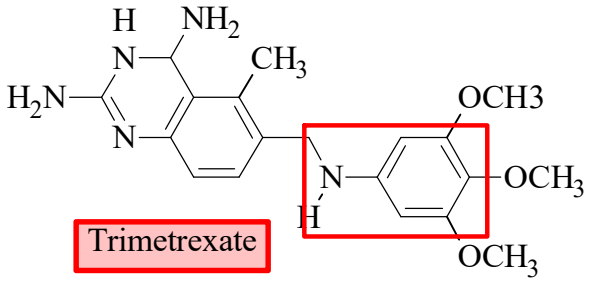
    pyrimethamine

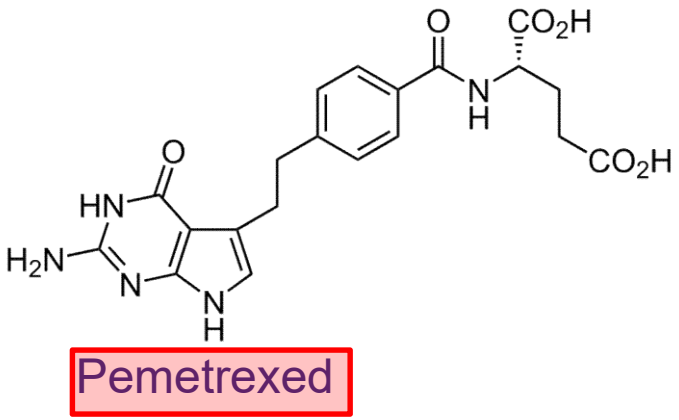
Compare Folic Acid, Pterine Like & Aryl-Pyrimidine as DHFR Inhibitors



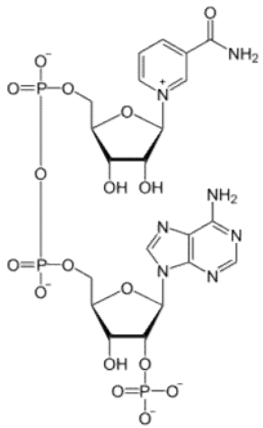


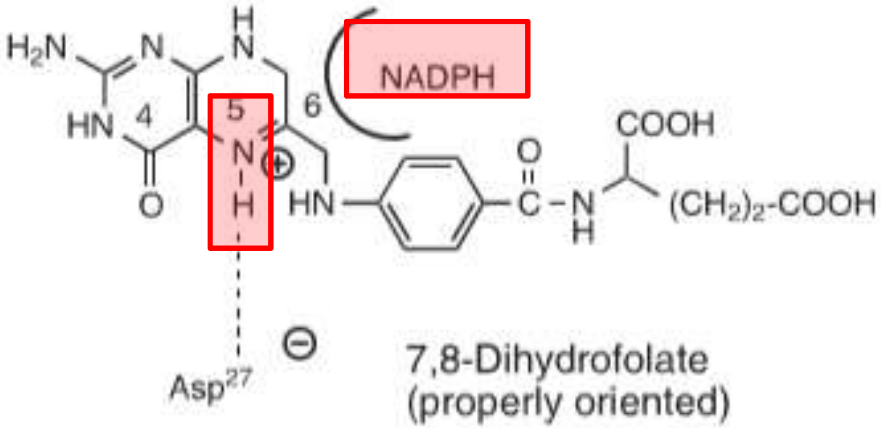




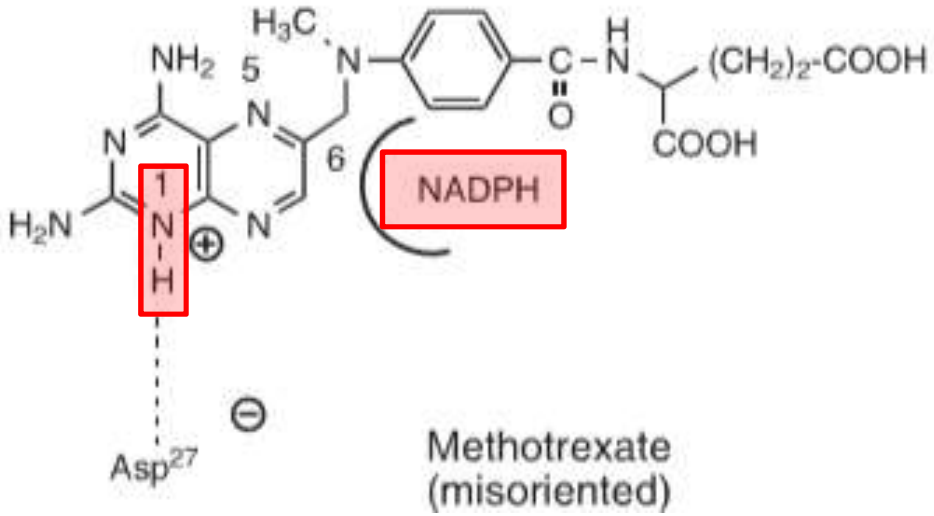


Compare Interaction Points of DHF & MTX to DHFR





- DHF:
  - ✓ N5: electron rich:
  - ✓ basic; protonation



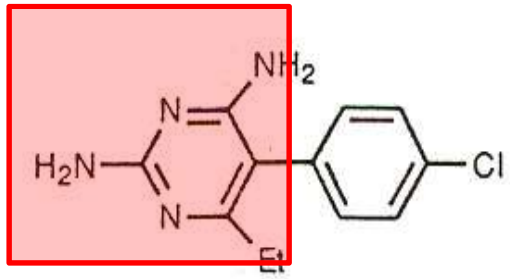
- MTX:
  - ✓ N1: electron rich:
  - ✓ Basic; protonation

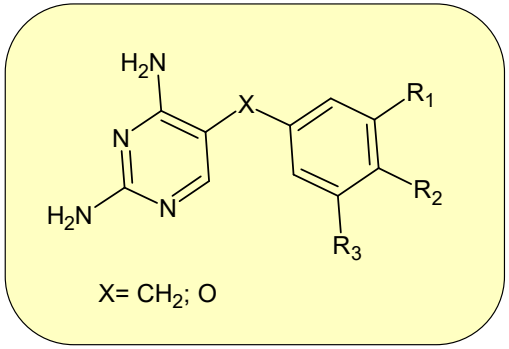
Figure 33.51 Misorientation of methotrexate at DHFR.

NADP/H: Nicotinamide Adenine Dinucleotide 2'-Phosphate/H

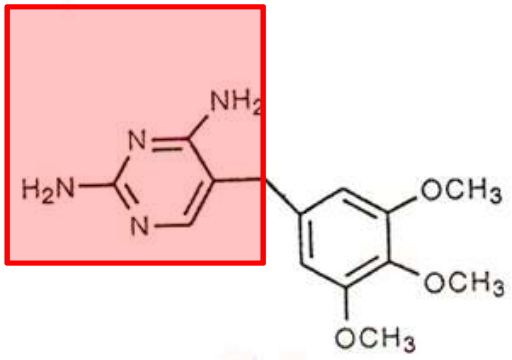
DHFRI: Non-Classic: Aryl-Pyrimidines: SAR

- Pyrimethamine





- Trimethoprim:



- Tetroxoprim

DHFRI: Aryl-Pyrimidines: Trimethoprim

- Introduced by Georg Hitching Noble & Gertrude Elion
- Nobel Prize in 1988
- Selectivity against bacterial DHFR: 10^5 times

✓ due to architectural difference

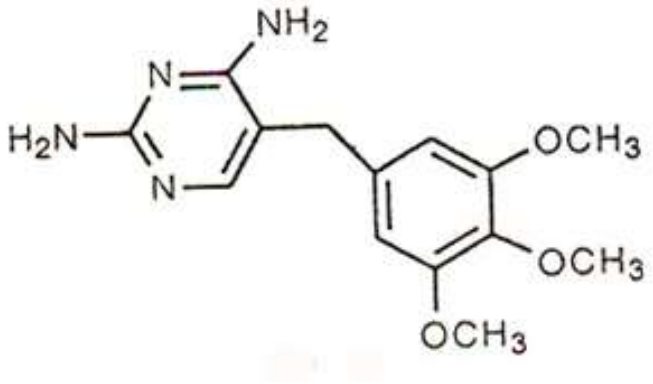
- Clinical indication:

✓ uncomplicated UTI caused by susceptible G^-

✓ otitis media

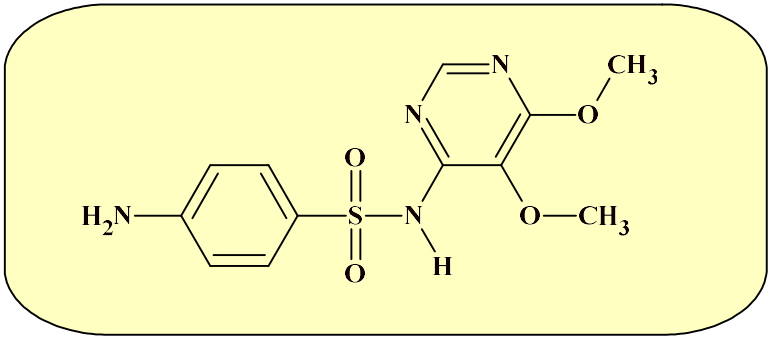
✓ traveler's diarrhea

✓ MRSA

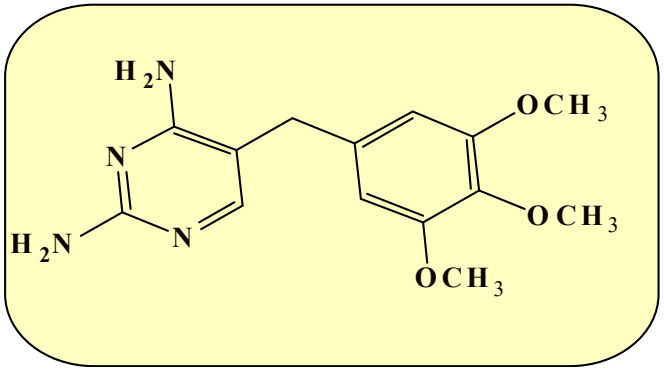


A Combinational Pharmaceutical Product: Fansidar®: Sulfadoxine: Trimpethoprim (20:1)

Sulfadoxine



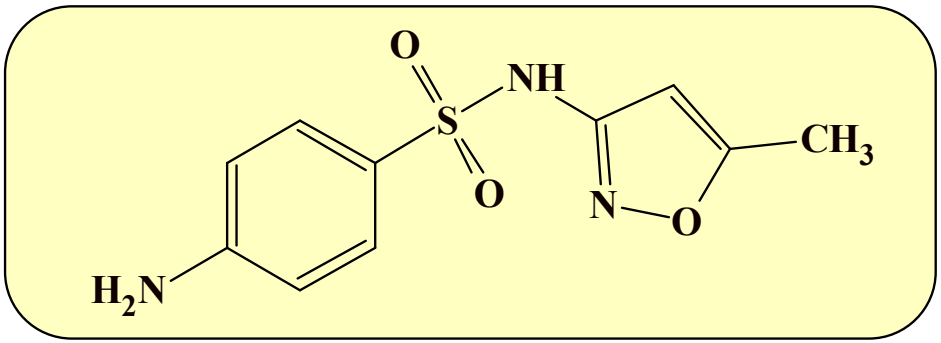
Trimpethopim



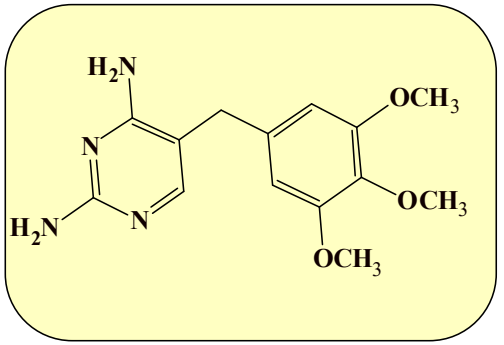
- Pharmacokinetic reasons to provide combinational dosage form.
- Provide 20:1 ratio in human body
- Subsequent blockade
- Synergistic & less likely to induce bacterial resistance
- Dosage form: tab.: 500 + 25 mg

A Combinational Pharmaceutical Product: Cotrimoxazole: Sulfamethoxazole: Trimpethoprim (5:1)

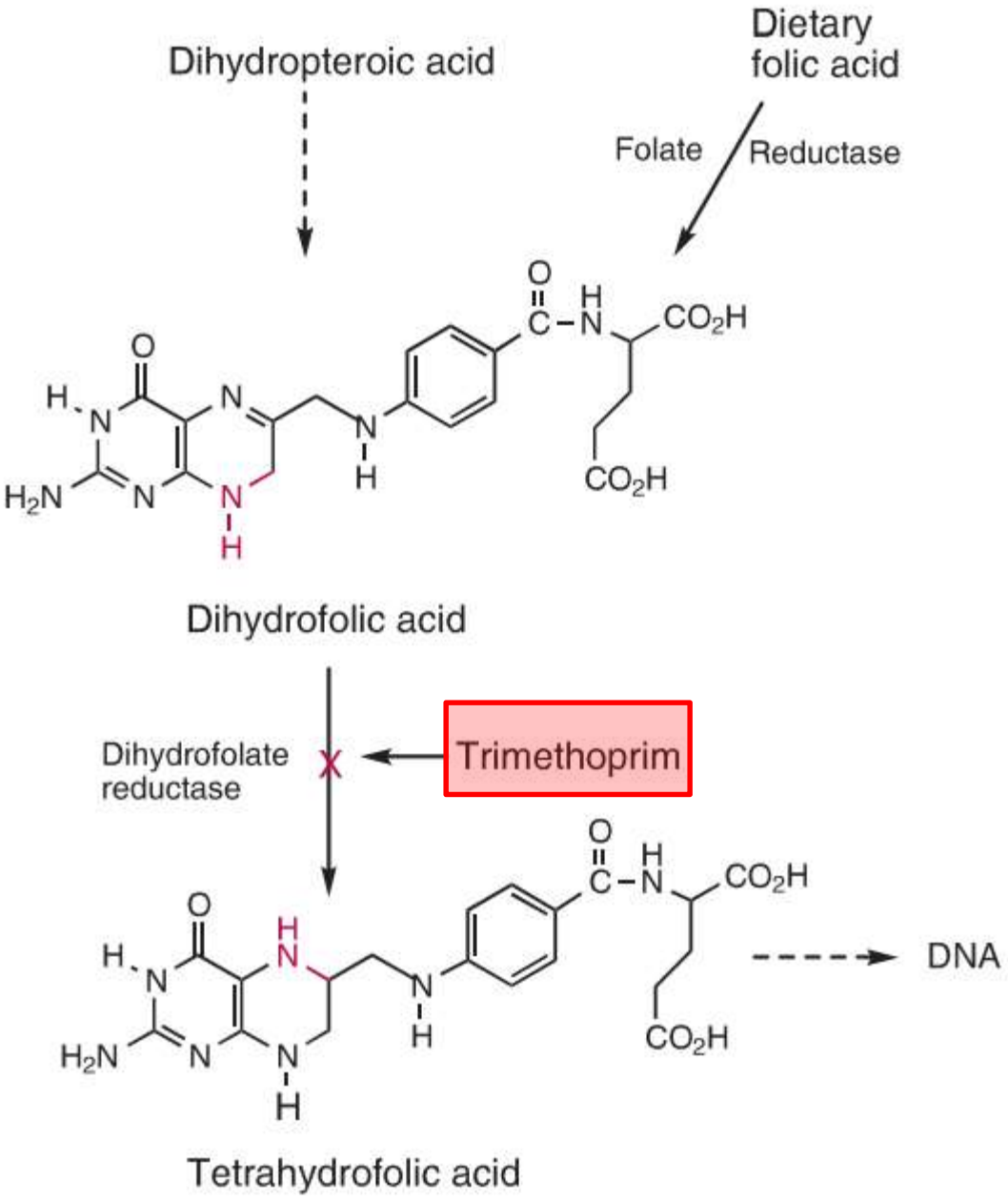
Sulfamethoxazole

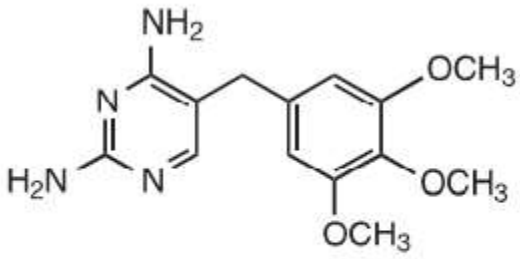


Trimpethopim



- Pharmacokinetic reasons to provide combinational dosage form.
- Provide 20:1 ratio in human body
- Subsequent blockade
- Synergistic & less likely to induce bacterial resistance
- Dosage forms: tab: 400 + 80 & 200 + 40 mg;
- suspension 200 + 40mg; inj.:80mg
- Trade names: Septrim®; Bactrim®



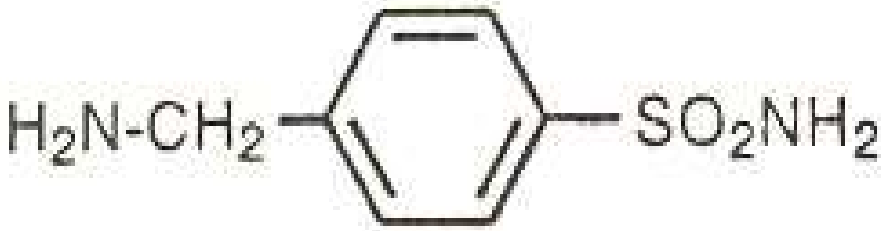


Trimethoprim

Figure 29.4 Site of action of trimethoprim.

A Homosulfanilamide: Mafenide

- Against Clostridium welchii
- Not effective by mouth

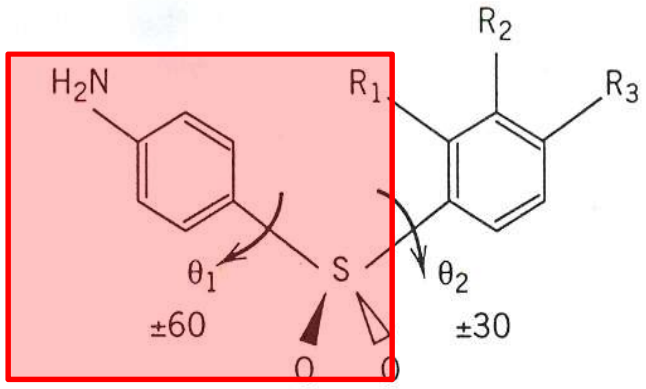


Sulfones

- Chemistry: 4,4'-Diamino-Diphenyl Sulfone (DDS)

✓ optimum conformation

- Follow the similarity & difference to sulfonamides.
- MOA:
- Clinical indication: against leprosy & leprea



Active conformations

Sulfones: Dapson Series